

Amendment and Response

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Applicant(s): Dominic E. COSGROVE
Serial No.: 09/970,318
Filed: 03 October 2001
For: IMMUNODIAGNOSTIC DETERMINATION OF USHER
SYNDROME TYPE IIA

Remarks

The final Office Action mailed 24 January 2005 has been received and reviewed. Claims 24-41 having been canceled, the pending claims are claims 1-23. Reconsideration and withdrawal of the rejections are respectfully requested.

Information Disclosure Statement

In follow up to the Supplemental Information Disclosure Statement filed on 09 November 2004, Applicant respectfully requests a copy of the considered and initialed 1449 form that listed U.S. Patent Numbers 6,660,485 B2 and 6,692,920 B1 be included with the next Official Communication.

The 35 U.S.C. §112, First Paragraph, Written Description Rejection

The Examiner rejected claims 1-23 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicant disagrees and traverses this rejection. Specifically, the Examiner asserted that, while the specification discloses antibodies immunoreactive with human usherin (SEQ ID NO:1, 2, and 4), the specification does not provide adequate written description for antibodies that bind to the human usherin protein *but do not cross-react with other non-usherin proteins within the biological sample* (pages 2-3 of the Office Action mailed January 24, 2005). The Examiner further asserted that "antibodies disclosed by the applicant that immunoreact with SEQ ID NO:2 would also immunoreact with laminins. In addition, there is no evidence provided by the applicant that would suggest that antibodies that immunoreact with SEQ ID NOs:1 and 2 would not cross-react with non-usherin proteins within the biological sample" (page 3 of the Office Action mailed January 24, 2005).

Applicant adamantly, yet respectfully, disagrees and submits that the Examiner's assertions are incorrect. As presented in the specification, antibodies to both SEQ ID NO:1 and SEQ ID NO:2 are "highly specific and useful for immunohistochemistry, immunoprecipitation, and western blotting" (page 22, lines 19-20 of the specification). By western blot analysis, both

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antibodies detect a single protein band of about 180 kilodaltons, the appropriate molecular size of usherin, in tissue extracts from testis, a tissue which expresses usherin, and not in tissue extracts from kidney, a tissue which does not express usherin (page 22, line 29 to page 23, line 3). The Examiner is further directed to Figure 5, showing results of the immunostaining of various tissues in which usherin is not expressed with an antibody to SEQ ID NO:2 (see page 7, lines 1-5, page 23, lines 3-4 of the specification). No usherin protein was detected in these tissues, including brain, skin, lung, skeletal muscle, smooth muscle, liver, and kidney, which do not express usherin (page 38, lines 6-8 of the specification). Identical results were obtained with an antibody to SEQ ID NO:1 (page 23, lines 3-4 of specification). Thus, as directly shown in the specification, antibodies that immunoreact with SEQ ID NOs:1 and 2 *DO NOT* cross-react with non-usherin proteins within a biological sample. In view of the specificity of antibodies to human usherin presented in the specification and discussed above, Applicant does not understand the Examiner's assertions that "antibodies disclosed by applicant that immunoreact with SEQ ID NO:2 would also immunoreact with laminins" and it is "unclear how antibodies that are immunoreactive to the usherin protein and not cross-reactive with non-usherin proteins would be obtained" (page 3 of Office Action mailed January 24, 2005). Applicant respectfully submits that the Examiner's assertions are in error.

Applicant respectfully submits that the specification provides adequate written description for antibodies immunoreactive with human usherin protein wherein the antibody does not cross-react with other non-usherin proteins within the biological sample. Withdrawal of this rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Enablement Rejection

Claims 1, 8, and 15 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserted that the specification does not reasonably provide enablement for a method of determining whether an

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individual has or is at risk for developing Usher syndrome type IIA. Applicant respectfully disagrees and traverses this rejection.

First, Applicant notes that claim 8 is drawn to "[a] method for detecting the presence or absence of an usherin protein." Claim 8 includes no recitations directed to "determining whether an individual has or is at risk for developing Usher syndrome type IIA." Thus, Applicant does not understand the inclusion of claim 8 in this rejection under 35 U.S.C. §112, first paragraph.

The Examiner asserted that while the claimed "method may very well be effective in determining whether an individual has or is at risk for developing Usher syndrome Type IIA, applicant has not provided any studies or experimental data that would support this assertion, or provided sufficient guidance such that studies on the effectiveness of the method could be performed without undue experimentation" (page 8 of the Office Action mailed January 24, 2005). The Examiner asserted that "the applicant does not provide any data involving the use of the antibodies in tissue samples from individuals with Usher syndrome Type IIA, rendering it unclear how well the antibodies would perform in determining individuals having or being at risk for Usher syndrome Type IIA" (page 4 of the Office Action mailed January 24, 2005).

Applicant respectfully disagrees and submits that it would not require undue experimentation to practice the claimed invention. "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed [and the] specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." See MPEP § 2164.02.

Further, in support of the methods of claims 1, 8, and 15, Applicant provides the information in paragraphs 4 to 8 and Figures A and B of the Declaration under 37 C.F.R. § 1.132 of Dominic E. Cosgrove, a copy of which is enclosed herewith. Briefly, to determine the feasibility of diagnosing Usherin syndrome type IIA using purified usherin antibody, immunohistochemical staining for usherin was carried out in basement membrane of minor

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salivary gland tissue obtained from five subjects with confirmed Usher syndrome type IIA. Archival minor salivary gland tissues from patients without Usher syndrome were used as control samples. The results are published in Cohn et al., Laryngoscope, 2004 114(7):1310-4, "Immunohistochemistry and reverse transcriptase-polymerase chain reaction as methods for diagnostic determination of usher syndrome type IIA."

The usherin-specific antibody used was developed by immunizing rabbits with the entire LN domain (amino acids 318 to 518) of human usherin (corresponding to SEQ ID NO:2 of the instant patent application) expressed using the FLAG-ATS system (Sigma, St. Louis, Missouri). This antibody is referred to as Antibody 2 in the instant patent application (see page 22, lines 19-30 of specification).

Figure A of the Declaration under 37 C.F.R. § 1.132 of Dominic E. Cosgrove shows normal salivary glands immunostained with antibodies specific for either usherin or type IV collagen. Hematoxylin and eosin (H&E) staining is provided for tissue visualization. Materials and methods are as detailed in Cohn et al., Laryngoscope, 2004 114(7):1310-4. Figure A demonstrates that usherin is present in the basement membranes of salivary gland tissue from normal individuals and co-localizes with collagen.

Figure B of the Declaration under 37 C.F.R. § 1.132 of Dominic E. Cosgrove shows the absence of usherin immunostaining in cryosections of minor salivary glands from a patient with Usher syndrome type IIA. Cryosections of minor salivary glands were immunostained using antibodies specific for usherin or type IV collagen. Four additional individuals were tested with similar results. Again, materials and methods are as detailed in Cohn et al., Laryngoscope, 2004 114(7):1310-4.

Applicant submits that one skilled in the art would conclude from the data in Figures A and B of the Declaration under 37 C.F.R. § 1.132 of Dominic E. Cosgrove that antibodies immunoreactive with human usherin can be used to successfully diagnose Usher syndrome type IIA. Applicant respectfully submits that the specification provides adequate guidance to enable one skilled in the art to which it pertains, or with which it is, most nearly

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connected, to make and/or use the invention of claims 1, 8, and 15 and that it would not require undue experimentation to practice the claimed invention. Reconsideration and withdrawal of this rejection under 35 U.S.C. §112, first paragraph is requested.

In rejecting claims 1, 8, and 15 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, the Examiner asserted that the specification fails to teach how to make antibodies immunoreactive with at least a portion of the protein having SEQ ID NO:4 that do not cross react with non-usherin proteins (page 4 of the Office Action mailed January 24, 2005). Applicant respectfully disagrees. The specification describes the complete amino acid sequence of the human usherin protein (SEQ ID NO:4). The specification describes immunization and screening methods for the production of antibodies highly specific for portions of the SEQ ID NO:4 protein that do not cross react with non-usherin proteins (see Example 1, pages 22-38 of the specification). Further, the specification characterizes two antibodies, antibodies to SEQ ID NO:1 and to SEQ ID NO:2, both of which are immunoreactive with the protein having SEQ ID NO:4 and do not cross react with non-usherin proteins (see page 7, lines 1-5, page 22, line 19 to page 23, line 5, and page 38, lines 6-8 of the specification). Applicant submits that the specification provides adequate guidance to allow one of skill in the art to make and use the antibodies of claims 1, 8, and 15. The Examiner asserted that the "applicant does not specify which epitopes of SEQ ID NO:4 are unique to the usherin protein so that antibodies specific only to usherin protein can be made" (page 4 of the Office Action mailed January 24, 2005). Applicant respectfully submits that such information is not necessary for the production of antibodies immunoreactive with at least a portion of the protein having SEQ ID NO:4 that do not cross react with non-usherin proteins.

In rejecting claims 1, 8, and 15 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, the Examiner further asserted "no evidence [is] provided by the applicant that would suggest that antibodies that immunoreact with SEQ ID NO:s 1 and 2 would not cross-react with non-usherin proteins within the biological sample" (page 4 of the Office Action mailed January 24, 2005) and that the applicant has failed to

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provide guidance for producing such antibodies (page 7 of the Office Action, mailed January 24, 2005). As discussed in the above response to the written description rejection of claims 1-23 under 35 U.S.C. §112, first paragraph, Applicant submits that these assertions are incorrect and submits that the specification provides adequate guidance for producing antibodies that are immunoreactive to the usherin protein and not cross-reactive with non-usherin proteins within the biological sample.

In rejecting claims 1, 8, and 15 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, the Examiner continues to assert that "the specification . . . states that the methods of the present invention provide for the use of antibodies that are immunoreactive with an usherin protein . . . as well as other polypeptides. . . . If the antibody forms an immunoconjugate with other polypeptides, false negatives would potentially be generated, as immunoconjugates would be present even though the usherin protein is not" (page 5 of the Office Action mailed January 24, 2005). Applicant does not understand the relevance of this assertion to the claims presently under examination. Claims 1-23 clearly recite "wherein the antibody which is immunoreactive with at least a portion of a human usherin protein having SEQ ID NO:4 *does not cross-react with other non-usherin proteins within the biological sample.*" While the specification might make mention of antibodies that are immunoreactive to proteins other than human usherin, the antibodies of claims 1-23 do "not cross-react with other non-usherin proteins within the biological sample." The Examiner is inappropriately reading the specification into the claims.

In rejecting claims 1, 8, and 15 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, the Examiner asserted that "usherin distribution in some tissues is very restricted, which could potentially generate false positives . . . applicant has not disclosed how prevalent the usherin protein is in the tissue, or the use of controls to ensure that any usherin protein present in the tissue will immunoreact with the antibodies" to support the assertion that "[t]his raises the question whether the method would actually be useful in determining whether an individual has or is at risk for developing Usher syndrome Type IIa"

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(page 8 of the Office Action mailed January 24, 2005). Applicant adamantly, yet respectfully, disagrees with these assertions.

First, Applicant directs the Examiner to Figures 4-6 of the specification, which disclose the distribution of usherin in various tissues. Figures 4 and 5 present a survey for usherin in various mouse tissues. Figure 4 demonstrates tissues in which usherin is expressed (page 6, lines 23-25 of the specification) and Figure 5 demonstrates tissues in which usherin is not expressed (see page 7, lines 1-2 of the specification). The results presented in Figures 4-5 confirm

usherin to be expressed in the basement membranes . . . of a large number of tissues, including the testis, epididymus, ovary, spleen, submaxillary gland, small intestine, and large intestine (Figure 4). No usherin expression was detected in the brain, skin, lung, skeletal muscle, smooth muscle, liver or kidney (Figure 5). Immunohistochemical localization of usherin is illustrated for tissue sections from the retina and the cochlea, which are tissues affected in USH2A pathogenesis (Figure 6). In the cochlea, usherin is expressed in virtually every basement membrane, as evidenced by complete co-localization with type IV collagen, which was used as a marker protein for basement membranes. Expression is particularly high in the strial capillary basement membranes (SCBM) (see arrows, Figure 6A and C). In the retina, usherin is again expressed in all of the basement membranes, based on complete co-localization with type IV collagen (Figure 6D and F). It is also very prevalent in the lens capsule and the Bruch's layer between the retinal pigment epithelium and the choroid layer which is very rich in basement membranes (The Bruch's layer of the retina is denoted by arrows in Figure 6D and F). At postnatal day 0 (p0) in the mouse, usherin is widely expressed in the basement membranes of the cochlea (Figure 6G).

See page 38, lines 3-23 of the specification. Figure 6 demonstrates the expression of usherin in the inner ear and eye of the mouse and in the human retina (page 7, lines 6-7 of the specification), demonstrating that usherin "localization is consistent from mice to humans" (page 38, lines 28-30 of the specification). The Examiner is directed to Pearsall et al., ("Usherin expression is highly conserved in mouse and human tissues," *Hear Res.* 2002 174(1-2):55-63) which substantiates the consistency of usherin expression in mouse and humans. In Pearsall et al. a "comparison of mouse and human tissues that stain positive or negative for usherin . . .

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shows that expression of usherin is 100% conserved between the two species except for the spleen" (p. 61, col. 2 and Table 1 of Pearsall et al.). "The location of usherin in human tissues directly parallels its location in the mouse, indicating that the regulation of tissue specific expression for this protein has been evolutionary (*sic*) conserved. This is especially evident in the tissues affected by mutations in the USH2A gene" (p. 62, col. 1 of Pearsall et al.). Applicant respectfully submits that the specification provides adequate guidance on the tissue distribution of usherin.

Second, Applicant submits, counter to the Examiner's assertions, appropriate controls have been included in all immunoassays with anti-usherin antibodies presented in the specification. The Examiner is directed to Figures 4-7 and page 38, line 3 to page 39, line 16 of the specification. Applicant submits that the specification provides adequate guidance for one of skill in the art to practice the claimed methods of determining whether an individual has or is at risk for developing Usher syndrome Type IIA.

Finally, Applicant again directs the Examiner to Pearsall et al., "Usherin expression is highly conserved in mouse and human tissues" (Hear Res. 2002 Dec;174(1-2):55-63), which acknowledges the diagnostic usefulness of the methods of the present invention:

To date, genetic testing and mutation detection are the only way to provide a definitive diagnosis in cases of Usher syndrome. This process can be very elaborate and time-consuming considering the large number of genes, the size of the genes, and the fact that several mutations are associated with the three types of Usher syndrome. Early detection of the disorder would optimize opportunity for effective intervention and treatment. If a patient has a family history of Usher II, immunoperoxidase staining of the patient's salivary glands dissected from an oral mucosa biopsy, could provide a cost and time effective way to diagnose a person with Usher IIA. The placenta of a newborn also contains usherin. Immunostaining of this tissue immediately after birth would provide a fast and completely non-invasive way to determine if an infant has Usher syndrome. This concept is particularly relevant now that newborn hearing screening programs have become commonplace in the United States.

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See page 62, col 2 to page 63. col. 1 of Pearsall et al., Hear Res. 2002 Dec;174(1-2):55-63,
"Usherin expression is highly conserved in mouse and human tissues."

For the reasons discussed above, Applicant submits that the specification provides adequate teaching and guidance for the claimed methods. Reconsideration and withdrawal of the rejection of claims 1, 8, and 15 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-23 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Dominic E. COSGROVE

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

April 25, 2005
Date

By: Nancy A. Johnson
Nancy A. JOHNSON
Reg. No. 47,266
Direct Dial (612) 305-4723

CERTIFICATE UNDER 37 CFR §1.10:

"Express Mail" mailing label number: EV 201 891 848 US Date of Deposit: 25 APRIL 2005

I hereby certify that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to: **Mail Stop RCE**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Sara E. Olson
Name: **SARA E. OLSON**
